

# Aripiprazole Augmentation Treatment in Treatment Resistant Bipolar Depression: Two Patient Reports



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## SUMMARY

It is known that in patients with bipolar disorder, depressive episodes last longer than mixed or manic/hypomanic episodes and there are reports detailing the difficulties confronted in its treatment. The concept of treatment resistant depression in bipolar disorder has not been as well described as that in treatment resistant unipolar depression. Here we present two patients with treatment resistant bipolar depression. The first patient in our study is a 51 year old woman whose diagnoses were bipolar disorder, depressive episode and multiple sclerosis (in remission with interferon treatment) at the time of augmentation with aripiprazole. The second patient is a 43 year old woman with bipolar disorder, depressive disorder without any comorbid illness at the time of augmentation with aripiprazole. Aripiprazole was administered variably between 20-30mg/daily based on tolerability and efficacy. In both cases, depression was assessed using the Hamilton Depression Rating scale (HDRS). Both patients responded to aripiprazole augmentation treatment. The effect of aripiprazole on bipolar depression needs to be further evaluated in double blind controlled studies. However, augmentation with aripiprazole in bipolar patients may be a future routine treatment for treatment resistant bipolar depression.

In this report, treatment of refractory bipolar depression and the efficacy of aripiprazole augmentation treatment in bipolar depression are discussed through two patients in depressive episode who remitted with aripiprazole augmentation

**Key words:** bipolar depression, treatment resistant, aripiprazole, augmentation

Bipolar disorder affects 1.7%-3.7% of the population. A diagnosis of bipolar disorder is made when a patient experiences periods of mania/hypomania with depression periods occurring frequently, with these periods being recurrent and severe (Martinez Aran et al. 2007). Together with subthreshold depressive symptoms, the duration of depressive periods are longer in bipolar patients (Kupka et al. 2007, Judd et al. 2008).

There is compelling evidence that clinical characteristics of bipolar depression apart from its treatment are different from those of unipolar depression (Akiskal 2005). Antidepressants can cause a manic shift or rapid cycling. Moreover, there is no strong evidence that antidepressants used commonly in bipolar depression are effective all the time and many of these drugs have been used in unipolar depression patients (Post et al 2003). It was reported that the efficacy of lithium is not sufficient in the management of bipolar depression

(Geddes et al. 2004). In the treatment of bipolar depression, only some antipsychotic drugs such as olanzapine, quetiapine and aripiprazole have been shown to be effective (Tohen et al. 2003, Calabrese et al. 2005, Dunn et al. 2008). Two case series have been published regarding the efficacy of aripiprazole in patients with bipolar depression refractory to aripiprazole (Kemp et al. 2007 a,b).

Depression is the longer lasting and more challenging stage of bipolar disorder, yet data on its management is inadequate. In view of this fact, it is not surprising to think that response to treatment may be poor and depression may be refractory to treatment. In the two cases below, aripiprazole augmentation treatment will be discussed in patients with treatment resistant bipolar depression. Written informed consent was obtained from the patients.

Received: 08.03.2011 - Accepted: 27.06.2011

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### First patient

The first patient in our study was a 51 year old female, married with two children. She was a house wife and graduate of secondary school. She had been followed since 1993 with the diagnosis of multiple sclerosis (MS). During her fourth MS attack, following corticosteroid treatment, in 2003, complaints started with talking too much, excitability, lack of sleep and excessive financial spending. They resolved spontaneously within three months. Then, a period started in which she received no pleasure from life, slept too much, heard voices giving commands such as kill yourself, and had suspicions that her spouse would harm her. The patient attempted suicide twice during this period. With the diagnosis of major depression with psychotic features, treatment with paroxetine, mirtazapine, risperidone and alprazolam was initiated. Initially her symptoms improved, however four months after beginning her initial treatment, she sought medical help again with the complaints of lack of pleasure from life, sleeping difficulty, lack of desire, and tiredness. Her family history revealed that her maternal aunt underwent outpatient treatment with the diagnosis of depression and her sister spends money frivolously, and is dynamic and energetic.

She received paroxetine 80mg/day (d), risperidone 2mg/d, lamotrigine 175mg/d, quetiapine 100mg/d, alprazolam 1mg/d, beta-glucan, and interferon beta 1a for the last four months and upon the failure of treatment, she was admitted to our clinic in 2007 for the first time.

Upon admission, the patient's HDRS score was 30. No pathology was found in routine biochemistry analysis. ECG and lung X-ray were normal. Her medication was discontinued and she underwent 7 sessions of electroconvulsive therapy (ECT). She was discharged with the diagnosis of 'bipolar disorder, severe depressive episode, without psychotic symptoms, MS in remission with a clinical global impression score of 2 and HDRS score of 8. Her medication at discharge was scheduled as follows: venlafaxine 150mg /d, quetiapine 200mg/d, lithium carbonate 900mg/d, clonazepam 2mg/d and beta glucan and interferon beta1 a as regular MS medication. In the control examination 10 days later, it was observed that her depressive symptoms were aggravated. HDRS score was found to be 25. There were no psychotic symptoms. In addition to other drugs, ziprasidone was started and the dose was increased to 120mg/d. When no improvement was seen in her condition four weeks later, ziprasidone was replaced with amisulpride and increased to 400mg/d. Symptoms were alleviated within one month and the HDRS score decreased to 15. However, upon the aggravation of her symptoms within two weeks, lamotrigine was added to her medication and gradually the dose was increased to 200mg/d. When no change was seen in her complaints, levothyroxine sodium 0.1mg/d was added. Meanwhile, the patient was also receiving lithium 1200mg/d, venlafaxine 225mg/d, amisulpride 200mg/d, lamotrigine 200mg/d, and clonazepam 1-2mg/d. Lithium level was 0.90meq/l. In her visit one month later, amisulpride was decreased and 10mg/d aripiprazol was

initiated. In one month, complaints improved at the rate of 50% of the HDRS. Amisulpride was interrupted and the dose of aripiprazole was increased to 15mg/d. Her HDRS score was 15. Aripiprazole was further increased to 20mg/day. One year after treatment started, her depression remitted. In the symptomless period, she experienced another MS attack and used corticosteroids for two months. During this period and within last two years, no new mood episodes have occurred in the patient. She is currently on venlafaxine 150mg/d, lithium carbonate 1200mg/d, lamotrigine 150mg/d and aripiprazole 20mg/d.

### Second patient

This second patient in our study is 43 year old married house wife. Approximately four years ago, after the death of her elder brother, complaints of withdrawal, lack of desire, sleeplessness and receiving no pleasure from life began. Despite the patient taking paroxetine and trazodone for two years, there was partial improvement and in August 2008 she was admitted to our clinic with then complaints of nervousness, aggressive behavior, talking too much, excessive spending and sleeplessness. The patient was diagnosed with no other physical disease, nor any family history of physical or psychiatric disease. She underwent seven sessions of ECT with the diagnosis of bipolar disorder (mania). The patient's condition resolved with sodium valproate 750mg/d and olanzapine 10mg/d. Three months after discharge, she was readmitted with feelings of guilt, suicidal ideations and psychomotor slowing; she then underwent nine sessions of ECT. She was discharged with venlafaxine 150mg/d, lithium carbonate 900mg/d, and lamotrigine 50mg/d, but her depression was aggravated one month later. Her lithium level was 0.82 mEq/l and drug doses were increased. Her symptoms did not improve in three months with a drug regimen consisting of venlafaxine 300mg/d, lithium carbonate 900mg/d, lamotrigine 150mg/d, and levothyroxine sodium 0.05mg/d, and her HDRS score was 27. As augmentation therapy aripiprazole 10mg/d was added. One month after the dose was increased to 15mg/d, her HDRS score was 20. Aripiprazole dose was increased to 20mg/d. In the control visit one month later, she stated that she started to miss people and did not feel guilty as in the past. Her HDRS score was 14 and after two months of follow up, aripiprazole dose was set at 30mg/d. The HDRS score became 5 after this dose; in six months of follow up our patient experienced complete remission. She is currently on venlafaxine 300mg/d, lithium carbonate 1200mg/d, lamotrigine 150mg/d and aripiprazole 30mg/d.

## DISCUSSION

The concept of resistance to treatment in bipolar depression is not as well defined as resistance in unipolar depression. In the first patient, it may be thought that both MS and the drugs used for its treatment (corticosteroids and interferon) may have contributed to the aggravation of symptoms. During corticosteroid treatment, affective symptoms, especially manic symp-

toms may appear. Nevertheless, it has been reported that these symptoms arise 3-7 days after the administration of steroids and resolve approximately 10 days after the withdrawal of corticosteroids (Brown et al. 2002). In our patient, her manic period started after stopping corticosteroid treatment. Therefore, it may be thought that her manic period was not drug related. Our patient has been on beta glucan and weekly intramuscular interferon beta 1a for about 15 years. No association of beta glucan with mood disorders was shown. The resistance to depression treatment may be related to interferon beta 1a. In various studies, it has been shown that depressive symptoms emerged 2-6 months after the initiation of interferon beta 1a (Mohr et al. 1999). It is also possible that the symptoms may be related to the severity of depressive symptoms before treatment rather than the administration of interferon beta 1a (Fehr et al. 2009). In the first of two randomized controlled studies, no difference was found between patients receiving interferon beta 1a and those receiving placebo in terms of depressive symptoms (Patten and Metz 2002) and in the second study, Beck Depression Inventory was administered to patients who have MS before the initiation of interferon beta 1a and 12 months after treatment with no difference (Zephyr et al. 2003). In view of these findings, there is no conclusive evidence that in patients with MS the use of interferon increases the risk of depressive disorder (Chwastiak and Ehde 2007). The first patient did not respond to two mood stabilizers, two group antidepressants, three different atypical antipsychotics and thyroid hormone augmentation treatment. In the second case, firstly the mania period began after 2 years of the depressive period and then, depression period started again after the mania period. The second depression period did not respond to two mood stabilizers, a double acting antidepressant and thyroid hormone augmentation treatment.

Post et al compared patients with bipolar disorder with patients who have major depressive disorder (MDD). They reported that of the cases they followed for one year following the treatment of patients in the acute period, 530 were excluded from the study due to depression. Further, they reported that in bipolar cases a lack of response to antidepressants was observed 1.6 times and a loss of response occurred 3.4 times more often than those with MDD (Post et al. 2003). In both of our cases, in order to treat depressive episodes, mood stabilizers, venlafaxine, atypical antipsychotics and L-thyroxine were used in combination with no response or only a partial response.

Although the neurobiological basis of efficacy of atypical antipsychotics in mood disorders still remains to be proven, it is thought that dopamine D2 and serotonin 5HT2A receptor blockage play a part. 5HT2A receptors are found in presynaptic dopaminergic neurons and the stimulation of these heteroreceptors prevent dopamine release, while their blockage induces dopamine release. Atypical antipsychotics are expected to increase dopamine levels by blocking 5HT2A receptors (Yatham et al. 2005). Aripiprazole is the only agent that has both antipsychotic and antimanic effects through partial agonism of D2 and 5HT2A (Keck and McElroy 2003). It is a 5HT2A antagonist at the same time. Its efficacy has been shown in acute mania and in the prevention of manic attacks (Uluşahin 2008, Yatham 2011). Moreover, it has also shown to be beneficial in the treatment of treatment resistant depression and anxiety when it is used to augment serotonin reuptake inhibitor treatment (Wortington et al. 2005), indicating that aripiprazole plays an important role in overcoming resistance to treatment via its double effect on dopamine and serotonin.

In a few open ended retrospective studies, it has been reported that in the inpatients diagnosed with bipolar depression, the addition of aripiprazole exerts favorable effects; but these findings have not been corroborated with double blind randomized studies (Ketter et al. 2006, McElroy et al. 2007, Sokolski 2007, and Dunn et al. 2008). However, the FDA approved the addition of aripiprazole to the treatment of unipolar depression and stated that it may also be useful in patients diagnosed with bipolar depression.

The previous psychotic mood episode history in our first patient, her having MS and using cortisone occasionally and regularly using interferon (Galeazzi et al. 2005), lack of response to antidepressants and mood stabilizers in both patients, partial response to ECT treatment, and frequent recurrence of depression are signs that the patients are treatment resistant. The observation of clinical improvement in both patients when aripiprazole was administered at 20-30mg/day doses suggests that augmentation with aripiprazole may be an effective treatment in refractory bipolar depression treatment just as in non-refractory bipolar depression cases or MDD cases. Further controlled studies with larger samples are required to clarify this issue.

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